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DOI: https://doi.org/10.1109/IEMBS.2010.5626763

Other titles: 32nd Annual International Conference of the IEEE EMBS Buenos Aires, Argentina, August 31 - September 4, 2010

Originally published at:
Wieser, M; Buetler, L; Koenig, A; Riener, R (2010). Quantitative description of the state of awareness of patients in vegetative and minimally conscious state. IEEE Engineering in Medicine and Biology Magazine, (1):5533-5536.
DOI: https://doi.org/10.1109/IEMBS.2010.5626763

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Quantitative Description of the State of Awareness of Patients in Vegetative and Minimally Conscious State

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Abstract— **Clinical scales represent the golden standard in characterizing awareness for patients in vegetative or in a minimally conscious state. Clinical scales suffer from problems of sensitivity, specificity, subjectivity, and inter-rater reliability. This leads to a misdiagnosis rate of up to 40% and consequences associated with inappropriate treatment decisions. In this study, objective measures including physiological and neurological signals are used to quantify the patient status. Using linear backward regression analysis, 13 variables (based on frequency analysis of the electrocardiogram, heart rate variability, amplitude and latency of the P300, skin conductance responses, changes in the blood pressure and respiration signal) were found to be sufficient to describe 74.7% of the variability of the scores. In this regression model, the P300, electrocardiogram and the blood pressure signal account for most of the variability. More patient data and additional measures will enable refinement of the methods. This new objective-measurement based model of the state of awareness will complement the clinical scales in order to increase the quality of diagnosis.**

I. Introduction

Clinical scales like the Glasgow Coma Scale (GCS), the JFK Coma Recovery Scale – revised (JFK CRS-r) or the Early Functional Abilities (EFA) are the golden standard describing the level of awareness of vegetative (VS) and minimally conscious state (MCS) patients [1-3]. However, it is known that the rate of misdiagnosis for these patients is up to 40% [4]. This can be explained by the inherent difficulties in detecting signs of awareness in patients with fluctuating arousal and perceptual, attentional and motor deficits. Because of this unsatisfactory situation many research groups are searching for new methods to detect and quantify the awareness in VS and MCS patients in order to reduce inappropriate treatment decisions.

Correlating the meaning of a single physiological or neurological signal to the awareness of VS and MCS patients has not been demonstrated to be an effective clinical tool [5-7]. Many recent studies have also shown that functional neuroimaging may serve an important role in classifying VS and MCS patients by identifying residual cognitive functions. Studies with positron emission tomography (PET) as well as functional magnetic resonance imaging (fMRI) have the potential to demonstrate distinct and specific reactions to controlled external stimulation without the need for any overt behavior (e.g. motor activities) by the patient, since the patient may be unable to comply with instructions. However, at present there is no validated objective clinical method to "measure consciousness" that can be used as a scale or as evidence of awareness [8].

In this study we combined the information obtained from several traditional clinical physiological signals in a resting condition and neurological signals based on an event related potential paradigm to quantify and describe the awareness of 8 patients in VS and MCS.

Manuscript received April 1, 2010. This work was supported by the National Center of Competence in Research (NCCR) on Neural Plasticity and Repair funded by the Swiss National Foundation (SNF) and the Gottfried & Julia Bangerter Rhyner Foundation.

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II. Methods

A. Patients

Eight patients (5 female and 3 male) who were an average age of 48.6 years (range: 20-66 years) and an average duration of 24 months (range: 3-71 months) after the incident were included in the study. The diagnoses of the participants included subarachnoid hemorrhage (3 patients), hypoxic brain damage (3 patients) and craniocerebral injury (2 patients). During the examination period GCS values of the patients were between 6 and 12.

The local ethics committee of Canton Thurgau, Switzerland, approved the study and a legal representative of each participant gave written informed consent. Task and testing procedures were in accordance with institutional guidelines and the study conformed to the Declaration of Helsinki. The measurements were conducted at the HUMAINE Clinic, Zihlschlacht, Switzerland.

B. Measurement System

All physiological signals (electrocardiogram (ECG), respiration signal, galvanic skin response (GSR) and blood pressure (BP)) were acquired with a PowerLab recording system from AD Instruments, Australia. For the ECG recording lead I and II of the Einthoven's triangle were used. A Piezo Respiratory Belt Transducer was used to monitor the breathing frequency. The transducer measured changes in thoracic or abdominal circumference during respiration in order to indicate the instances of inhalation and expiration as well as breathing strength. Two bipolar GSR finger electrodes together with a GSR amplifier of low voltage and 75Hz AC excitation were used to obtain the GSR signal. The continuous BP signal was acquired noninvasively by using a CNAP Monitor 500 from CNSystems AG, Austria. The monitor provides beat-to-beat values for systolic, diastolic and mean BP. All signals are transferred to and synchronized in the PowerLab system. The software package Chart Pro from AD Instruments, Australia, was used to acquire and store the data with a sampling frequency of 1 kHz.

The event related potentials (ERP) were obtained from 3 scalp electrodes using a SynAmps^2 amplifier system from Compumedics Neuroscan, Germany. Silver-silver-chloride electrodes were used in combination with a SynAmps^2 Quick-Cap from Compumedics Neuroscan, Germany. Electrodes were placed in the Fz, Cz and Pz positions according to the international 10-20 electrode placement standard. The reference electrode was placed between the locations Cz and CPz. The electrooculogram (EOG) was recorded from two pairs of bipolar electrodes. The software package Scan 4.2 from Compumedics Neuroscan, Germany, was used to record and store the acquired data. Electrode impedance was kept below 10kΩ and data were sampled at 1 kHz. For the synchronization and presentation of the tone stimulus Stim^2 software and earphones from Compumedics Neuroscan, Germany, were used.

C. *Protocol*

All participants were measured weekly over an 8 week period. Each measurement session contained one resting and one stimulation period which were randomized. Subjects were in a supine position during the entire experimental session. The duration of the resting period was 7 minutes and additionally in the stimulation phase, patients were presented with a classical P300 tone paradigm. The paradigm consists of 200 stimuli; the standard stimulus (500 Hz) was presented in 85% and the deviant stimulus (1000 Hz) in 15% of the cases. All physiological and neurological signals were continually recorded throughout the experiment.

In addition, the patients were examined and evaluated using the clinical scales GCS, JFK CRS-r and EFA within 24 hours before or following each measurement session.

D. *Acquired Signals and Variables*

The acquired signals ECG, respiration, GSR and BP were only analyzed for 7 min. resting period, whereas, the stimulation period was exclusively used for the evaluation of the ERP (P300). Data were preprocessed using a Butterworth 2nd order bandpass filter of 1-30 Hz.

1) *ECG:*

The two ECG leads were merged to one complex lead by differentiating and summing of the two recorded ones. The absolute values of the complex lead were compared to an adaptive threshold [9] and time intervals between heartbeats (known as RR intervals) were detected. (variables: HR_rate and the standard deviation HR_rateStd).

The Poincaré plot, a technique based on the ECG signal and taken from nonlinear dynamics, reflects the nature of the fluctuations of the RR intervals. The plot takes a sequence of intervals and plots each interval against the following one. So, the statistical correlation between consecutive intervals is displayed in a graphical manner. This analysis of heart rate variability (HRV) provides summary information (variable: HR_area) as well as detailed beat-to-beat information on the behavior of the heart (variables: HR_SD1 and HR_SD2). HRV is an excellent technique to study cardiovascular tone in patients with neurological injuries [10].

The sympathetic and parasympathetic balance of the autonomic nervous system is also reflected in the HRV. A common frequency domain method is the application of the discrete Fourier transform to the series of RR intervals. This provides an estimation of the amount of variation at specific frequencies. The High Frequency band (HF) can be found between 0.15 and 0.4 Hz (variable: HR_HF). HF appears to derive mainly from vagal activity or the parasympathetic nervous system. The Low Frequency band (LF) is defined between 0.04 and 0.15 Hz (variable: HR_LF). LF derives from both parasympathetic and sympathetic activity and is assumed to reflect the delay in the baroreceptor loop. The ratio of low-to-high frequency spectral power (LF/HF) is used as an index of sympathetic to parasympathetic balance of heart rate fluctuation (variable: HR_LFHF).

Additional analysis was based on the Very Low Frequency band (VLF), the RMS and standard deviations as well as the total power in the ECG signal (variables: HR_VLF, HR_SDNN, HR_RMSSD, HR_totalP).

2) *Respiration:*

For the given respiration flow signal the peaks (end of inhale) and the troughs (end of exhale) were identified. So, the average respiration rate (variable: Resp_frequ) and the standard deviation of the duration of the breaths (variable: Resp_frequStd) could be calculated. A slow and regular breathing pattern comprised information about the patient's physical constitution because patients in VS and MCS show respiratory instabilities [11]. The average duration of the inhale and exhale phase (variables: Resp_Inh, Resp_Exh) and the ratio of the two phases were determined (variable: Resp_InhExh). The tidal volume was estimated from the flow signal by numerical integration (variable: Resp_Area).

3) GSR:

According to [12] arousal and activity are reflected in electrodermal activity and can be measured via skin conductance level. Specific events within the GSR signal are known as "skin conductance responses". At these events the curve suddenly rises within 4s to a peak value greater than 0.02 μS and then starts to fall again. The number of detected events during the resting period was counted. (variable: GSR_event).

4) BP:

Analyzing the blood pressure signal the maxima (systolic BP) and the minima (diastolic BP) were identified and the estimated value of the mean arterial BP (MAP) as well as the difference was calculated (variable: BP_sys, BP_dias, BP_MAP and BP_pulse with their standard deviation).

Further, the duration of the pulse wave between the minimum and the maximum value (from diastolic BP to the systolic BP value) was determined (variable: BP_Time2Peak). The blood pressure signals were obtained via a pressure cuff attached to the index and middle finger and, therefore, this value includes information about cardiac output as well as vessel elasticity.

5) EEG:

The recorded EEG data were further processed using the BrainVision Analyzer software package from Brainproducts, Germany. EEG data were bandpass filtered from 1.5-30 Hz (2nd order Butterworth filter) and ocular artifacts were corrected applying an independent component analysis (ICA) algorithm provided by the BrainVision software. Thereafter, EEG data were searched for epochs containing artifacts that exceed ±100μV at any electrode. Those epochs were also excluded from subsequent analysis.

For analyzing individual auditory related potentials, the EEG signal during acoustic stimulation is cut into epochs of 1s including a 100ms baseline correction prior to stimulus onset. Segments were averaged relative to the stimulus and the electrode position. Peak amplitudes and latencies are exported and post processed for a subsequent statistical analysis (variables: P300_Fz_amp, P300_Cz_amp, P300_Pz_amp and P300_Fz_lat, P300_Cz_lat, P300_Pz_lat as well as the average values P300_amp, P300_lat and an overall score P300_score).

E. Quantitative Description

A linear regression was used to get a quantitative description of the state of awareness. Linear regression analysis estimates the coefficients of a linear equation, involving several independent variables that best predict the value of a dependent variable. As the dependent variable the average of two clinical scales JFK CRS-r and EFA was used. For that purpose both scales were normalized (normalized range: 0 to 100) in order to average the relative change of the scores. All variables regarding the analysis of the physiological and neurological signals were used as independent variables.

Before linear regression was applied tests were performed whether the distribution of the independent variables is normal and whether the variables are linearly independent. Redundant variables were removed and the remaining not normally distributed variables were transformed in order to get normal distribution.

Backward method was used to start with all remaining independent normally distributed variables and reduce the set of variables stepwise with the criterion: probability of F-to-remove ≥ 0.1. Finally, the acceptability of the model as well as the goodness of fit were tested with an ANOVA (analysis of variance) and the R-squared value and the pattern of residuals was inspected.

III. Results

After testing normal distribution and cross correlation of 36 variables (presented in "D. Acquired Signals and Variables") only 20 variables remained and 5 out of these 20 were ln-transformed in order to reach a normal distribution.

Linear backward regression was applied to the variables and the adjusted R-squared was maximal with 13 variables: P300_Fz_lat, P300_Pz_lat, BP_pulse, ln(HR_LF), HR_totalP, ln(HR_area), P300_Cz_amp, P300_Pz_amp, BP_MAP, P300_Cz_lat, P300_score, ln(Resp_InhExh) and ln(GSR_event). The proportion of variation in the dependent variable explained by the regression model is expressed by the value of the adjusted R-squared of 0.747. Further, an ANOVA was performed to test the acceptability of the model from a statistical point of view. The null hypothesis that all the population values for the regression coefficients are zero could be declined ($F=14.06$ and $p<0.001$).

To determine the importance of the variables the standardized coefficients were evaluated. The ERP variables P300_Fz_lat and P300_Pz_lat and the remaining BP variable BP_pulse followed by the ECG variables ln(HR_LF), HR_totalP, ln(HR_area) had the highest impact (-0.83, -0.79, 0.74, -0.62, 0.56, -0.53, respectively). Therefore, in this model variables regarding P300, BP and ECG contribute most to the description of the clinical scores.

Finally, figure 1 shows the normalized change of the clinical scales compared to the used model containing 13 variables. Data are based on one patient over a period of 8 weeks.

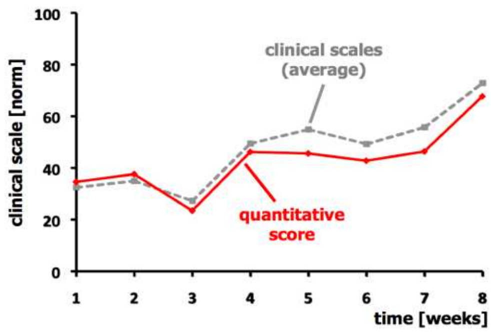

Fig. 1. Normalized change of the averaged scores of the clinical scales JFK CRS-r and EFA. Data are based on one patient over 8 weeks and the quantitative score is based on 13 variables.

IV. Discussion

The results showed that 13 variables are sufficient to explain 74.7% of the variability of the averaged and normalized clinical scales. The clinical scales are the gold standard yet they suffer from problems of sensitivity, specificity, subjectivity, and inter-rater reliability. To address this problem we used two different clinical scales (JFK CRS-r and EFA) and took the average of the normalized change as our dependent variable in order to reduce uncertainty of the scale values. Results herein find an adjusted R squared of 74.7%; findings are quite promising, although, limitations of this study include the fact that data are based upon 8 patients with varied medical conditions, which is representative for this population. Further patient analysis will improve understanding of the clinical value of the objective metric. So, this new objective-measurement based model will complement the clinical scores in order to improve the quality of the diagnosis.

It could also be shown that the variables concerning the P300 (P300_Cz_amp, P300_Pz_lat) have the highest correlation coefficients with the averaged and normalized clinical scales (Pearson correlation: 0.473 and -0.303, respectively). Therefore, it seems to be plausible that these variables contribute strongly to the regression model. One of the final goals is the reduction of the amount of measurements while sustaining the quality of the quantitative description. It seems that the P300 as well as the ECG and BP signals are crucial measurements, whereas, the respiration or the GSR signal are less important signals. To confirm this assumption more analysis will be necessary.

V. Conclusion and Outlook

Using linear backward regression 13 variables were sufficient to explain 74.7% of the variability of the change of the clinical scores JFK CRS-r and EFA. Variables based on P300, ECG and BP account for most of the variability.

More patient data and additional measures will enable refinement of the methods and additional classifications to be incorporated into the new objective-measurement based model of the state of awareness. Further, additional statistical methods such as linear mixed models and evaluation measurements in a second hospital will be applied to improve and elucidate the data for applications in a clinical context.

Acknowledgment

Special thanks to Gery Colombo, Heike Vallery and Kit August for their technical support as well as Clemens Gutknecht, Josef Ludwig Schönberger, Jenny Haefeli, Angela Bonetti, Ximena Omlin and Romy Rodriguez del Rio for their clinical support during the study.

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